REMARKS

Applicant respectfully requests entry of the Amendment and reconsideration of the claims. Claim 8 has been amended and claims 20-29 have been added. The specification has been amended to update application information. Upon entry of the amendment, claims 1-16 and 20-29 will be pending. Claims 1-7 and 11-16 have been withdrawn from consideration by the Examiner. Support for the added claims can be found in the specification, on page 3, lines 12-19; Example 1; Figures 4; and in the claims as originally filed. Applicant submits the amendments do not raise any issues of new matter.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or withdrawn claims or to any subject matter pursued in a related application. Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Utility

Claim 8 was rejected under 35 U.S.C. § 101 as lacking patentable utility. The Examiner alleges the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection.

Claim 8 as amended is drawn to a transgenic mouse whose genome comprises a null platelet-activating factor receptor (PAFR) allele. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . " Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. . .
>
> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

> . . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.
>
> (MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

> *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.
>
> Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.
>
> (MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts.

> Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone,

> serve as a basis for challenging the asserted utility under 35 U.S.C. 101.
>
> (MPEP 2107.02, III(B)(emphasis in original and added).

The Guidelines additionally provide that:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).
>
> (MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility should not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
>
> . . .
>
> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
>
> . . .

> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.
>
> (p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.
>
> (p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

> Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.
>
> (preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

> The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.
>
> (p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

> Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.
>
> Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

In addition, commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, at least three (3) large pharmaceutical company have ordered the presently claimed mouse. This acceptance more than satisfies the practical utility requirement of section 101 as **it cannot be reasonably argued that a claimed invention, which is actually being used by those skilled in the art, has no "real world" use**. (see, for example, Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success); (Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand.")

As evidence of such sales and purpose of such use, attached hereto is a Rule 132 Declaration from Robert Driscoll, Vice President of Intellectual Property & Legal Affairs of Assignee, Deltagen.

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice. Utility of the claimed knockout mouse would be apparent to, and considered credible by, one of skill in the art, as the role of knockout mice in studying any of these conditions is both specific and substantial.

The Examiner argues that the phenotypes do not correlate with human disease (page 5). The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proffered by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ

367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated specific phenotypes. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated.

Definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to satisfying the utility requirement. It is enough that the claimed mouse demonstrates phenotypes, relative to a wild type control mouse, and that knockout mice are recognized in the art as models for determining gene function, both in mice and in humans. According to Austin et al.:

> Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome

> supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
>
> (p. 921)(emphasis added).

In addition, as pointed out by Doetschman, one clearly skilled in the art, (*Laboratory Animal Science* 49:137-143, 137 (1999)(copy attached), the phenotypes observed in mice do correlate to gene function:

> The conclusions will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function, that we should let the unexpected phenotypes lead us to the specific cell, tissue, organ culture, and whole animal experiments that are relevant to the function of the genes in question, and that the absence of phenotype indicates that we have not discovered where or how to look for a phenotype.
>
> (emphasis added).

In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

The Examiner alleges the specification does not distinguish the F and N generation in Table 1 or teach the strain of the wild-type control. Applicant does not agree. Table 1 at page 52 of the specification clearly shows the F and N generation (either F2N0 or F2N1) for the control mice and homozygous mutant mice. The observed phenotypes are relative to wild-type control mice. According to the protocol (which is presented in the DeltaBase commercial database), comparison was made with age, gender and strain-matched control mice. Thus, the **backgrounds of the control mice and the claimed transgenic mice are identical**. Applicant is willing to provide affidavits regarding the control mice background if required by the Examiner.

The Examiner alleges the results of the open field test do not correlate to a useful phenotype. Applicant does not agree and submits decreased anxiety is a useful phenotype. The open field provides a novel environment that creates an approach-avoidance conflict situation in which the animal desires to explore, yet instinctively seeks to protect itself. The chamber is

lighted in the center and has no places to hide other than the corners. A normal mouse typically spends more time in the corners and around the periphery than it does in the center. Normal mice however, will venture into the central regions as they explore the chamber. Anxious mice spend most of their time in the corners, with almost no exploration of the center, whereas bold mice travel more, and show less preference for the periphery versus the central regions of the chamber. Identification of genes associated with anxiety have real world use for measuring anxiety levels and evaluating the effectiveness of anti-anxiolytic drugs. See, for example, the specification at page 23, lines 26-27.

The Examiner asserts only 2 PAFR -/- mice and 2 control mice were tested and that the phenotype is ambiguous and the data flawed because one PAFR -/- mouse spent more time in the central region of the field than the control mouse. Applicant does not agree. The number of mice tested is provided in Table 1 in the column labeled "Count". Three F2N0 +/+ mice, nine F2N1 +/+, six F2N0 -/- mice, and eleven F2N1 -/- mice were tested in the open field assay. There were no significant differences between N0 generation homozygous mutants and their N0 generation wildtype littermates. Homozygous mutant mice from the N1 generation spent significantly more time in the central region on the open field test than their N1 generation wildtype littermates. This indicates less anxiety in N1 generation homozygous mutants compared to their N1 generation wild-type littermates. Applicant therefore submits the phenotype is not ambiguous because the data and conclusions based on the data are not flawed.

The Examiner alleges the specification does not distinguish the F and N generation in Table 2 or teach the strain of the wild-type control. Applicant does not agree. Similar to Table 1, Table 2 at page 53 of the specification clearly shows the F and N generation (either F2N0 or F2N1) for the control mice and homozygous mutant mice. As discussed above, the homozygous mutant mice were compared with age, gender and strain-matched control mice. Applicant is willing to provide affidavits regarding the control mice background if required by the Examiner.

The Examiner alleges the results of the hot plate test do not correlate to a useful phenotype. Applicant does not agree and submits increased pain threshold is a useful phenotype. The hot plate analgesia test is designed to indicate an animal's sensitivity to a painful stimulus. In Deltagen's protocol, the mouse is placed on hot plate, and its latency to pick up and lick or fan a hindpaw is recorded. Alterations in latency to hind paw licking indicate changes in pain

thresholds. Identification of genes associated with pain and pain threshold have real world use for evaluating a nociceptive disorder. See, for example, the specification at page 26, lines 9-12.

The Examiner asserts only 2 PAFR -/- mice and 2 control mice were tested and that the pain threshold phenotype is based on statistically insignificant data. Applicant does not agree. The number of mice tested is provided in Table 2 in the column labeled "Count". Six F2N0 +/+ mice, twelve F2N1 +/+, eight F2N0 -/- mice, and eleven F2N1 -/- mice were tested in the hot plate assay. There were no significant differences between N0 generation homozygous mutants and their N0 generation wildtype littermates. Homozygous mutant mice from the N1 generation displayed an increased response latency to lick or fan their hindpaw on the hot plate test compared to their N1 generation wildtype littermates. This indicates N1 generation homozygous mutants had higher pain threshold compared to their N1 generation wild-type littermates. Applicant therefore submits the phenotype is not ambiguous because the data supporting the phenotype is statistically significant.

The Examiner alleges that mice without PAFR cannot be used to identify agents that act on PAFR because the mice do not express PAFR. Applicant does not agree. The claimed mice can be used to determine the specificity and toxicity of drugs by comparison with wild-type mice (see, for example, new claim 26). In addition, heterozygous mice do express the PAFR gene.

The Examiner argues that the asserted utility is not substantial or credible because the specification does not identify any compounds.

The Examiner's requirement that, in order to patent a mouse, Applicant must correlate decreased anxiety or increased pain threshold with a disease in humans is similar to the Patent Office's position that was struck down in *In re Brana*.

The Examiner notes that while the mutant mice may have "scientific utility." scientific utility is not "patentable utility" or a "well established utility" (page 5). Applicant does not agree and submits that if using the mice to study gene function has scientific utility, then it necessarily has patentable utility. According to the MPEP, if an "assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (MPEP § 2107, II (A)(3); II (B)(1)). If it is well known to those skilled in the art that KO mice are useful for determining gene function, then those skilled in the art would certainly regard such use as credible, substantial and specific. Nothing more is required to satisfy the statutory requirement of patentability.

The Examiner argues that the asserted utility is neither specific nor substantial, citing Olsen and Bowery (pp. 6-7).

According to the MPEP:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
>
> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

(MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

> Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). Thus, the cited portions of the MPEP guidelines relate to the situation where further research is required to establish or confirm any utility. Such is not the case here. As acknowledged by the Examiner, knockout mice have a well-known use in the study of gene function. In the present case, the present invention does not require further research to establish a utility. Applicant has determined that the PAFR gene is associated with, for example, decreased anxiety and increased pain threshold. The Applicant has provided an immediate benefit to the public – as demonstrated by the transfer of the claimed invention to at least one large pharmaceutical company. Whether additional research is required to identify drugs capable of targeting the PAFR receptor or gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

The Examiner cites Olsen for the proposition that the disruption in the gene "may" be the result of other genes compensating for the PAFR disruption.

First, the Examiner's argument is based on conjecture, not fact. Second, even if true, whether PAFR directly or indirectly causes these phenotypes is irrelevant – a drug targeting the gene or protein would have the same effect – directly or indirectly. Third, Olsen clearly does not support the Examiner's position that such knockout mice have no utility.

Olsen states that "gene targeting is useful in delineating the contribution of a given gene product to phenotypic characteristics" even though "some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype" (emphasis added). In fact, even with respect to GABA genes, Olsen concludes that "the use of mutant and knockout mice has aided understanding of the roles of GAD and GABAR in the intact mammalian organism, with much promise for additional information to come" (Olsen at 91). Even with respect to mice having increased lethality, Olsen states: "[t]he γ2 and β3 subunit knockouts are associated with early postnatal lethality but have nonetheless provided considerable new information about their importance, include relevance to neurodevelopment, synaptogenesis, and possibly human disease. The β3 is a strong candidate for involvement in the epilepsy and other phenotypic attributes of Angelman syndrome, a human genetic disorder characterized by mental retardation, seizures, motor incoordination, and sleep disturbances. The γ2L knockout has allowed direct testing and negation of the selective subunit hypothesis for ethanol modulation of GABAR function. The δ subunit knockout appears to provide information about the function of GABAR in adult cerebellum, dentate gyrus of the hippocampal formation, and the thalamus. GAD_{65}, GABAR β3, and GABAR δ subunit knockouts all exhibit spontaneous seizures, but of different sorts, confirming suspicions that GABAR malfunction might produce epilepsy by more than one mechanism and providing excellent animals models for investigation of the cause of the seizure phenotype." (Olsen at 91-2).

Olsen goes further: "[i]n summary, transgenic and knockout mice have demonstrated that GABA plays a major role in brain development, control of palate formation, and epileptogenesis via multiple mechanisms." (Olsen at 92). It is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well accepted use. In the present case, the claimed PAFR null mouse demonstrates phenotypes. Olsen would agree that such mice are clearly useful.

The Examiner cites Bowery for the proposition that "the advent of GABA-B1 knockout mice has also failed to provide support for multiple receptor types" and concludes that although drugs may be identified which bind to the GABA or PAFR, the "agent may not treat disease."

Bowery clearly does not support the Examiner's position. For example, Bowery discusses use of hot-plate, tail-flick and paw pressure protocols to evaluate acute pain behavior in GABA-B1 null mutant mice. Based on the reported data, Bowery concludes "it is likely that GABA-B-mediated effects do indeed exert a tonic control of nociceptive processes in the naïve animal" (p. 255, col.2). Thus, Bowery supports the utility of knockout mice in evaluating the role of GABA genes.

Regarding Mombereau, the Examiner argues that antagonists were not found using the mice but were found using *in vitro* assays. Applicant submits it is well accepted in the art to use *in vitro* screening methods to identify potential agents prior to verifying the potency, safety, specificity and other pharmaco properties *in vivo*. The important point here is that Mombereau used the mice in pharmacological studies: he found them useful. It is irrelevant at what stage the claimed mice are used in the drug discovery process.

Regarding commercial sales, the Applicant has cited case law and a well-respected treatise to support the legal position that sales are evidence of patentable utility as they clearly show a "real world" use and acceptance by those skilled in the art. The Examiner cites *Schoenwald* for the proposition that "providing evidence that a product was known in the art was not evidence that the product had patentable utility" (p. 11). *Schoenwald* does not stand for the proposition cited by the Examiner. In fact, the utility requirement was not at issue. The case involved the novelty of a claimed composition that was described in a prior art reference. The court held that the reference need not recite a utility in order to anticipate the claimed composition.

In addition to their use in studying gene function, the claimed transgenic mice are useful for studying gene expression. The mice within the scope of the amended claims contain a visible marker such as GFP. Their use in studying gene expression is clearly recognized by those skilled in the art:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point

for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 922)(emphasis in original; emphasis added)(copy attached). Applicant respectfully reminds Examiner that a claimed invention need only satisfy one of its stated objectives to satisfy the utility and enablement requirements.

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying PAFR gene function with respect to the cited phenotypes, expression analysis, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

Enablement

Claim 8 was rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner alleges one skilled in the art would not know how to use the claimed invention because the claimed invention lacks a specific or substantial asserted utility or a well established utility for the reasons set forth in the utility rejection. Applicant respectfully traverses the rejection.

For the reasons set forth above, Applicant submits the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the claimed invention. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution

of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

5-2-05
Date

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